

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/445, 9/00, 47/48</b>		A1	(11) International Publication Number: <b>WO 95/20964</b> (43) International Publication Date: <b>10 August 1995 (10.08.95)</b>
(21) International Application Number: <b>PCT/EP95/00319</b> (22) International Filing Date: <b>30 January 1995 (30.01.95)</b>  (30) Priority Data: <b>9402029.4 3 February 1994 (03.02.94) GB</b>		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).  Published <i>With international search report.</i>	
(71) Applicant <i>(for all designated States except US)</i> : SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).  (72) Inventors; and (75) Inventors/Applicants <i>(for US only)</i> : LEONARD, Graham, Stanley [GB/GB]; SmithKline Beecham Pharmaceuticals, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB). COOPER, David [GB/GB]; SmithKline Beecham Pharmaceuticals, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).  (74) Agent: LAWTON, Peter, Phillip; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).			
(54) Title: <b>ORAL LIQUID COMPOSITIONS CONTAINING PAROXETINE RESINATE</b>			
(57) Abstract  An oral liquid pharmaceutical composition comprising a paroxetine-Amberlite IRP88 complex.			

**FOR THE PURPOSES OF INFORMATION ONLY**

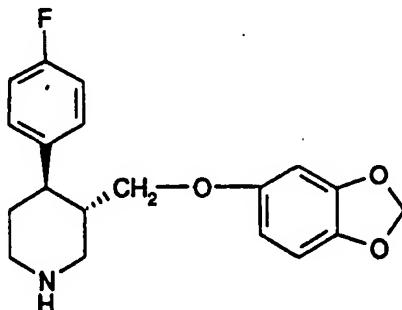
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

## ORAL LIQUID COMPOSITIONS CONTAINING PAROXETINE RESINATE

The present invention relates to novel formulations and to the use of such a formulation in the treatment and/or prevention of certain disorders.

5 US Patent 4,007,196 describes certain compounds which possess anti-depressant activity. One specific compound mentioned in this patent is known as paroxetine and which has the following formula:



10

This compound has been approved for human use and is being sold in many countries around the world as an anti-depressant agent.

All paroxetine sold to date has been in the form of oral swallow tablets.

15 Many physicians have expressed a desire to be able to prescribe an oral liquid containing paroxetine and some have even made their own oral liquid by crushing conventional swallow tablets and mixing them with water. There are however, a number of draw-backs to this oral liquid, firstly paroxetine has a very bitter taste which is highly noticeable when administered as an oral liquid, secondly such oral liquids have poor stability qualities and have a shelf-life of only a few days.

20 WO 91/13612 relates to the sustained release of pharmaceuticals using compositions in which the drug is complexed with an ion-exchange resin. The specific ion-exchange resin described in this published patent application is Amberlite IRP-69.

25 When Amberlite IRP-69 is used to complex with paroxetine it was found that whilst the taste was effectively masked the composition had an unacceptably low bioavailability when compared to a swallow tablet.

It has now been found that Amberlite IRP-88 can be used to form a stable taste masked complex with paroxetine and which complex has acceptable bioavailability when compared to the conventional swallow tablet.

30 Accordingly, the present invention provides an oral liquid pharmaceutical composition comprising a paroxetine - Amberlite IRP-88 complex.

Amberlite IRP-88 is commercially available from Rohm & Haas in a pharmaceutically acceptable grade.

The oral liquid pharmaceutical composition is prepared in conventional manner such as by mixing paroxetine and Amberlite IRP-88 together in an aqueous medium. Suitably the IRP-88 and paroxetine are present in a ratio of 1:1 to 2:1. It should be appreciated that superior taste masking properties are obtained with a 2:1

5 ratio.

Other pharmaceutically acceptable excipients may also be added such as thickeners such as Keltrol and/or Avicel (in particular Avicel CL 611); dispersants such as propylene glycol; moisture retaining agents such as glycerol; sweetners such as sorbitol and sodium saccharin buffering agents such as citric acid and sodium citrate; preservatives such as sodium benzoate and mixtures of methyl and propyl parabens (parahydroxybenzoates), artificial colours such as F D and C Yellow No. 6 Sunset Yellow; flavouring such as Givaudan Natural Orange and/or Lemon; and antifoaming agents such as silicone anti-foam.

10 Preferably the amounts of buffering agents are controlled to give a pH of 4 to 6. Most preferably a pH of 4.5 to 6.0.

15 The amount of paroxetine used is adjusted such that in a single unit dose there is a therapeutically effective amount of paroxetine. Preferably the unit dose contains from 10 to 100 mg paroxetine (as measured in terms of the free base). More preferable the amount of paroxetine in a unit dose is 10mg, 20mg, 30mg, 40mg or 20 50mg. The most preferred amount of paroxetine in a unit dose is 20mg of paroxetine. Preferably the volume of liquid in a unit dose is in the range 5 to 20ml most preferably 10ml.

25 Preferably paroxetine used in the formulation is in the form of the hydrochloride hemi-hydrate which may be prepared according to the procedures outlined in US Patent 4,721,723.

Suitable procedures for preparing paroxetine include those mentioned in US Patents 4,009,196, 4,902,801, 4,861,893 and 5,039,803 and PCT/GB 93/00721.

30 It has been mentioned that paroxetine has particular utility in the treatment of depression, paroxetine may also be used in the treatment of mixed anxiety and depression, obsessive compulsive disorders, panic, pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia and the depression arising from pre-menstrual tension and adolescence.

35 The present invention therefore also provides a method of treating or preventing any of the above disorders which comprises administering an effective or prophylactic amount of an oral liquid pharmaceutical composition comprising a paroxetine-Amberlite IRP-88 complex to a sufferer in need thereof.

The present invention further provides the use of an oral liquid pharmaceutical composition comprising a paroxetine-Amberlite IRP-88 complex in the manufacture of a medicament for treating or preventing the above disorders.

The present invention yet further provides a pharmaceutical composition for use in the treatment or prevention of the above disorders which comprises a paroxetine-Amberlite IRP-88 complex admixed with a pharmaceutically acceptable carrier.

5 The following examples illustrate the present invention:

**Example 1 (1:1) Ratio of Amberlite IRP-88 to paroxetine.**

	mg/10 ml
Paroxetine hydrochloride †	22.8
Amberlite IRP 88 (< 63 µm)	22.8
Keltrol	40.0
Propylene Glycol	350.0
Glycerol	350.0
Sorbitol (70%)	4000.0
Citric acid	15.0
Sodium Citrate	10.0
Sodium benzoate	10.0
Sodium Saccharin	5.0
Sunset Yellow	0.5
Givaudan Natural Orange	1.0
Givaudan Natural Lemon	2.0
Antifoam Silicone	20.0
Water	to 10.0

10

**Example 2 (2:1) Ratio of Amberlite IRP to paroxetine**

	mg/10ml
Paroxetine hydrochloride (< 180 microns)	22.8
Amberlite IRP 88 (< 200 mesh)	40.0*
Avicel CL 611	300.0
Propylene Glycol	500.0
Glycerol	500.0
Sorbitol (70%)	4000.0
Citric acid (anhydrous)	15.0

Sodium Citrate (dihydrate)	10.0
Methyl parahydroxybenzoate	20.0
Propyl parahydroxybenzoate	6.0
Sodium Saccharin	5.0
FD&C Yellow No. 6	0.9
Givaudan Natural Orange 74388-74	1.0 mcl
Givaudan Natural Lemon 74940-74	2.0 mcl
Silicone Antifoam 1510	20.0
Water	10.0

\* on an Anhydrous basis

**Example 3**

5

As above but 40.0 mg was replaced with 300 mg of Avicel CL 611.

**Example 4**

10 As above but 15 mg of Keltrol and 300 mg of Avicel CL 611 was used.

**Claims**

1. An oral liquid pharmaceutical composition comprising a paroxetine - Amberlite IRP-88 complex.
- 5 2. A process for preparing a pharmaceutical composition as defined in claim 1 which process comprises mixing paroxetine and Amberlite IRP-88 together in aqueous medium.
- 10 3. A process according to claim 2 in which the molar ratio of IRP 88 to paroxetine is 1:1 to 2:1.
- 15 4. A pharmaceutical composition according to claim 1 in which any one or more of the following is added; thickeners, dispersants, moisture retaining agents, sweeteners, buffering agents, preservatives, artificial colours, flavourings and anti-foaming agents.
5. A pharmaceutical composition according to claim 4 in which the amount of buffering agents are controlled to give a pH of 4 to 6.
- 20 6. A pharmaceutical composition according to any one of claims 1, 4 or 5 which is in the form of a unit dose.
7. A pharmaceutical composition according to claim 6 in which the amount of paroxetine in the unit dose is 10mg, 20mg, 30mg, 40mg, or 50mg.
- 25 8. A pharmaceutical composition according to claims 1 or 4 to 7 in which the paroxetine is in the form of the hydrochloride hemihydrate.
- 30 9. A method of treating or preventing mixed anxiety and depression, obsessive compulsive disorders, panic, pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia and depression arising from pre-menstrual tension and adolescence which comprises administering an effective or prophylactic amount of an oral liquid pharmaceutical composition as defined in claim 1. According to any one of claims 1 and 4 to 8 to a sufferer in need thereof.
- 35 10. The use of an oral liquid pharmaceutical composition as defined in claim 1 comprising a paroxetine-Amberlite IRP-88 complex in the manufacture of medicament for treating or preventing mixed anxiety and depression, obsessive

compulsive disorders, panic, pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia and depression arising from pre-menstrual tension and adolescence.

11. A pharmaceutical composition as defined in claim 1 for use in the treatment or  
5 prevention of anxiety and depression, obsessive compulsive disorders, panic, pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia and depression arising from pre-menstrual tension and adolescence.

# INTERNATIONAL SEARCH REPORT

Intern. Application No  
PCT/EP 95/00319

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K31/445 A61K9/00 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR,A,2 215 233 (A/S FERROSAN) 23 August 1974 cited in the application see claims 1,10 see page 10, line 24 - line 27 ---	1-11
A	WO,A,91 13612 (BEECHAM GROUP P.L.C.) 19 September 1991 cited in the application see claims see page 5, line 9 - line 21 see example 3 -----	1-11

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*'A' document defining the general state of the art which is not considered to be of particular relevance
- \*'E' earlier document but published on or after the international filing date
- \*'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*'O' document referring to an oral disclosure, use, exhibition or other means
- \*'P' document published prior to the international filing date but later than the priority date claimed

\*'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*'Z' document member of the same patent family

Date of the actual completion of the international search

21 April 1995

Date of mailing of the international search report

04.05.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentiaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Scarpioni, U

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/EP 95/00319

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 1-8, 10-11 because they relate to subject matter not required to be searched by this Authority, namely:  
**REMARK: although claim 9 is directed to a method of treatment of the human body by therapy (Rule 39.1(IV)PCT), the search has been carried out and based upon the alleged effects of the composition.**
2.  Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

Internat. Application No  
PCT/EP 95/00319

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR-A-2215233	23-08-74	GB-A-	1422263	21-01-76
		AT-B-	333759	10-12-76
		BE-A-	810310	16-05-74
		CA-A-	1038390	12-09-78
		CH-A-	592059	14-10-77
		DE-A-	2404113	08-08-74
		JP-C-	1268487	10-06-85
		JP-A-	49101385	25-09-74
		JP-B-	59046216	10-11-84
		JP-C-	1272362	11-07-85
		JP-A-	58174363	13-10-83
		JP-B-	59048826	29-11-84
		LU-A-	88398	04-05-94
		LU-A-	69264	10-04-74
		NL-A-	7401189	01-08-74
		SE-B-	401827	29-05-78
		US-A-	3912743	14-10-75
		US-A-	4007196	08-02-77
<hr/>				
WO-A-9113612	19-09-91	AT-T-	117893	15-02-95
		AU-B-	643263	11-11-93
		AU-A-	7348391	10-10-91
		DE-D-	69107202	16-03-95
		EP-A-	0519950	30-12-92
		JP-T-	5504574	15-07-93
<hr/>				